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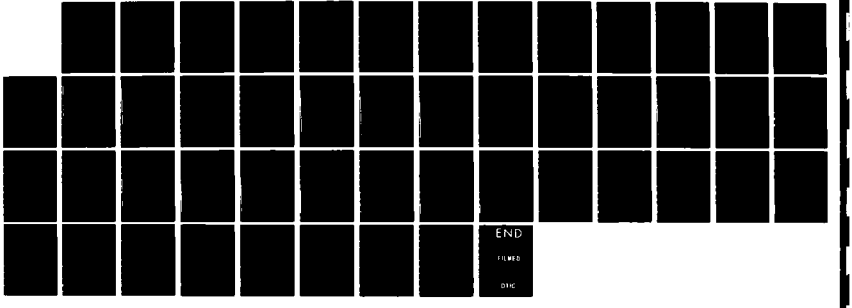

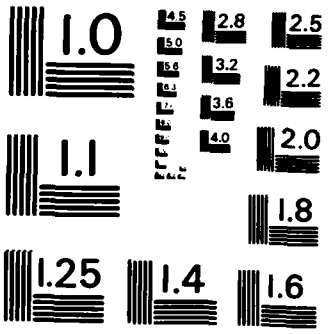

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A PROPOSAL FOR A LONGITUDINAL STUDY TO ASSESS THE HAZARDS OF RADIATION IN SPACE FLIGHT

Glen Irving Reeves, M.D.
The University of Texas
Health Science Center at Houston
School of Public Health, 1985

Supervising Professor: Spurgeon Neel, M.D., M.P.H.

This proposal involves the establishment of a registry of all United States astronauts, past and future, plus non-astronaut controls. The registry will record the incidences of malignant neoplastic disease and diabetes mellitus, and the space radiation exposure received. Data will be carefully analyzed to see if there is a dose-related increase in these diseases related to the exposure to ionizing radiation, with an eventual goal of establishing reliable risk estimates related to dose received.

The history of cancer related to radiation exposure is summarized, and the space radiation environment briefly described. Physiological changes accompanying space flight and their potential effects on radiation tolerance and carcinogenesis are discussed. The reasons why data from animal experiments and human occupational, medical, and nuclear weapon exposure cannot be extrapolated to the long term health risks of astronauts are discussed at length, and the study instruments for establishing a long term descriptive surveillance study are described.

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A PROPOSAL FOR A LONGITUDINAL STUDY TO ASSESS THE HAZARDS OF RADIATION IN SPACE FLIGHT

By

GLEN IRVING REEVES, M.D.

THESIS

Presented to the Faculty of The University of Texas
Health Science Center at Houston
School of Public Health
in Partial Fulfillment
of the Requirements
for the Degree of

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THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT HOUSTON
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Houston, Texas
June 1985

A PROPOSAL FOR A LONGITUDINAL STUDY TO ASSESS THE HAZARDS OF RADIATION IN SPACE FLIGHT

By

GLEN IRVING REEVES, M.D.

APPROVED:

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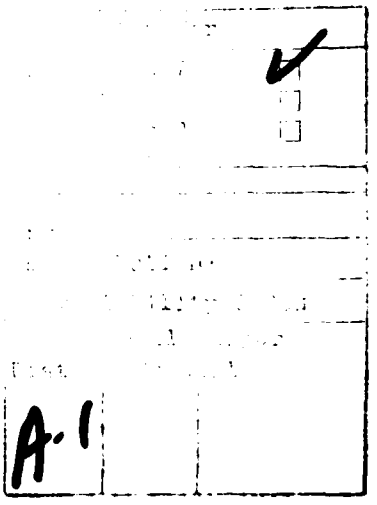

INTRODUCTION

The immediate objective of the proposed study is to set up a registry to record the necessary data to establish the relationship between radiation exposure in space and occurence of conditions known or suspected to be associated with radiation exposure, primarily neoplastic disease (especially malignant), and also diabetes mellitus, and possible unanticipated radiation-related illnesses and causes of death. The ultimate objective is to determine the types and dose-related magnitude of the effects of space radiation to set up a data base against the time when we will ultimately desire to go farther into the solar system, and perhaps beyond.

The major hypothesis underlying the study is that, since ionizing radiation is a known carcinogen, there will be a dose-related increase in cancer incidence. Based on the information acquired in the study, we will be able to make recommendations to individual astronauts in the future regarding the medical risks of the radiation exposure they have and are projected to receive. Also, with this information regarding the medical risks combined with probabilities of exposure based on the launch date, projected trajectory, time in solar cycle, length of flight, etc., we can, for longer missions and distant missions, help determine what protective modifications of shielding, passive and active, need to be made before missions are launched.

Assumptions underlying the study are: 1) we can't duplicate the nature and types of space radiation exposure through

terrestrial studies with respect to dose rate, the mixture of particulate and photon radiation, high atomic number particles (HZE), and high energies; 2) we can't reliably extrapolate from data from space-irradiated animals to man for long-latency diseases such as cancer at the low doses these animals receive; 3) although human epidemiological studies regarding radiation-related cancer induction are invaluable in helping to set up a study such as this one, their data are not applicable to space flight exposures; 4) we can't duplicate certain synergistic and antagonistic factors affecting physiologic responses to space radiation exposure such as vibration, acceleration, weight loss, erythrocyte mass loss, and especially weightlessness on earth.

The importance of this study rests on the fact that space radiation is a primary source of hazard for orbital and interplanetary space flight[32]. Increasing numbers of people will be going into space in the next several years, particularly as the economic value of space flight to private business increases[50]. Concern over the risk of cancer on the basis of occupational exposure is high, and most likely will increase. The best way by far to estimate the quantitative risks of space radiation is through a longitudinal observational study designed to observe adverse effects and relate them to dose exposures. Else we run the ethically impermissible risk of eventually finding adverse long term effects occurring at undesirable rates with no reliable way of prescribing acceptable dose levels for future astronauts.

BACKGROUND AND LITERATURE REVIEW

On December 22, 1895, Wilhelm Roentgen took the first X-ray photograph, of his wife's hand, and mailed prints to several associates for a New Year's Day present. Only a month later Emil H. Grubbe, a Chicago pharmacist-homeopath, displayed radiation-induced transient erythema of his hand. Not to be deterred, on January 29 he treated probably the first cancer patient with the new rays[36]. The first major complication was in April 1896 when an American physician, Dr. John Daniel, caused epilation of the scalp of his dean! The first occupational injury was probably to Dr. Gustav Kaiser, who retired from his X-ray clinic due to radiodermatitis of his hands. His successor, Dr. Guido Holtzknecht, also developed radiodermatitis of his hands. After many lesser surgical procedures for this very painful condition, he eventually underwent complete amputation of his right hand and much of his left. He died an agonizing death at age 53, presumably from complications of vascular thrombosis[37]. It became apparent that the new "Roentgen rays" could cause not only transient, immediate effects, but also create even more serious conditions that became apparent and permanent after a long latency period.

The occupational hazards of ionizing radiation were studied early on. A study of male British radiologists practicing before and after 1921, when the British X-ray and Radium Protection Commission issued its first formal recommendations, showed that death rates from cancer, particularly of the skin and pancreas, and also cancer of the lung and leukemia, were higher in radiologists

than in other British males of the higher socioeconomic classes and males in general before 1921. After 1921, the reverse was true[12]. However, another study showed that American radiologists had higher cancer death rates than other physicians, though this difference decreased with time[30].

Attempts to quantitate low-dose effects of ionizing radiation are very difficult, as most human radiobiological data has been obtained at higher dose levels and under different conditions than those seen in space flight and other occupational settings. Most, but not all, radiobiologists feel that there is probably no threshold dose for carcinogenesis; even a very small dose increases the risk of carcinogenesis over the "normal" risk[7,10,15,22,23,43]. However, this statement applies to carcinogenesis only at doses which do not cause sufficient damage to induce other factors known to affect tumor induction such as immunosuppression, compensatory cellular proliferation, or other effects stemming from tissue destruction[7]. In other words, although the physicochemical and subcellular biological effects of ionizing radiation are gradually becoming clearer, no one knows whether radiation introduces, at very low doses, protective or inhibitory effects at the tissue level that would suppress cells that had been damaged to the point of becoming carcinogenic.

Most data for the quantification of biological effects, in this case carcinogenesis, at low dose levels come from extrapolations from data obtained in treating patients with menorrhagia, ankylosing spondylitis, mastitis, tuberculosis, and from victims of

the weapons exploded at Hiroshima and Nagasaki. Based on these and other data many sources have given a rough estimate of the increased risk of cancer in a lifetime to be around one case per ten thousand person-years per rem[7,9,10,22,28,41,48]. But even if this figure were accurate, it is based on data from persons receiving a few exposures to single high doses of usually monoenergetic photon radiation. Astronauts, on the other hand, receive continuous low-dose and low dose-rate radiation from photons and particles of several types and energies.

As the dose rate is reduced, the cell-killing potential of radiation decreases. Below about one rad/minute there is little dose-rate effect because almost all sublethal damage is repaired; cell-killing (and presumably latent effects such as carcinogenesis also) is due to non-repairable injury[19]. Clinical treatments usually deliver several rads per minute. At very low dose rates (a few rads/day) proliferating cells, which initially decrease their mitotic rates, eventually return to normal rates of proliferation[19]. The reticuloendothelial system in rats receiving 0.25 rad/day for one year actually showed increased activity; one study even showed a longer life span in mice receiving 30 rads/day for 20 days[21]: Of course I do not wish to imply that very low dose rates of radiation are actually beneficial! I do wish to emphasize the inadvisability of applying standards based on total dose received at high dose rates to radiation received at low dose rates, such as encountered in space.

The effects of the type of irradiation on carcinogenesis

are little known, but what evidence we have indicates that the types and incidence rates of certain neoplasms vary depending upon what type of radiation is encountered, as well as the dose. An increased incidence of leukemia was noted at Hiroshima in those receiving over 10 rads of radiation compared with nonexposed persons and those receiving less than 10 rads; the incidence rates increased linearly with total dose received. At Nagasaki, however, this dose-related increase was not seen until 100 rads. The lymphoma rate was increased in both cities but more so in Hiroshima; also, the types of lymphoma encountered were different. This is quite possibly due to the increased neutron dosage at Hiroshima[20]. It is known that the protective effects of tissue hypoxia seen with photon irradiation are not nearly as prominent with neutrons[19], that the repair of potentially lethal damage does not occur with neutrons[20], and that the relative biological effectiveness (RBE) and linear energy transfer (LET) differ from photon irradiation, depending not only upon neutron energy but upon the specific tissue being studied[16]. Also, the more fractionated the neutron dose, the greater the effect, unlike photon irradiation.

Protons are very seldom used in clinical radiation therapy, as they deposit a large amount of energy in a relatively small volume of tissue, thus making sterilization of a large and ill-defined tumor mass difficult. In addition, adequate sized beams for clinical or experimental use are difficult to construct. Protons induce different types of neoplasms in monkeys than do photons; a large series of monkeys given proton irradiation of

differing energies at different doses had unusually high incidences of gliomas, according to Lt Col David Wood, the current officer in charge of the surviving colony, which is housed at Brooks Air Force Base, Texas[52]. Proton-irradiated mice had increased incidences of sarcomas, particularly in the colon and small intestine[18]. The RBE, with respect to tumor induction, varied with respect to the proton energy and specific neoplasm induced from photon irradiation. The incidences of diabetes mellitus and endometriosis, conditions not usually associated with radiation in man, were increased in the monkeys. Since diabetes can be a severe illness causing or contributing to death, based on these studies it appears advisable to record its incidence in astronauts exposed to proton irradiation, despite lack of evidence in human studies to date linking it with radiation exposure. Because of the different LET patterns between protons and photons, and the differing depths of organs in monkeys and man, these data are very difficult to extrapolate to man[4]. Under space conditions Soviet and American astronauts found they could measure doses from protons of energies under 10 MeV (million electron volts) fairly consistently, but not above this level. Interestingly enough the Soviets assigned a quality factor (QF) of 4.9 to protons under 10 MeV; we assigned a QF of 2.95[6]. Yet the LD_{50}'s of protons are probably less than for photons[18,52]. Consequently, although the various spectra of proton energies have been fairly well mapped out[8], and are probably the most significant sources of radiation damage over most orbital altitudes and inclinations[49]. their biological significance in terms of carcino-

genesis in man is not very well understood at all, nor is likely to be under terrestrial experimental conditions.

Extrapolations from animal data to human conditions are not at all straightforward. Owing to the large numbers needed for low-dose carcinogenesis studies, mice are the animals most frequently studied. Yet one study indicated the survival time in the control mice varied from 550-700 days, depending upon what month the shipments were received[21]! Documentation of the "life span shortening" effects of radiation becomes pretty difficult! Laboratory animals vary from man with respect to size, rates of metabolism, life span, relative placement of organs within the body, and responsiveness to the acute effects of radiation. The most reliable data by far for long term radiation effects in man have to be from epidemiological studies. Animal and <u>in vitro</u> experiments are of great value in studying pathogenic mechanisms of carcinogenesis; they are unreliable for quantitative risk estimates of human radiation exposure.

Since 1957 it has become apparent that the radiation space environment is very complex and nonuniform in terms of photons and particles of various energies, layers of high energy charged particles (the Van Allen Radiation Belts, or VARB), a continual background of isotropic radiation originating outside the solar system (galactic cosmic radiation, or GCR), and solar cosmic radiation (SCR) associated with the solar cycle with occasional highly radioactive flares. Moreover, the radiation background changes with time. Unfortunately the types of

radiation responsible for the largest dose contributions in spacecraft (protons, albedo neutrons, and cascades of photons and electrons generated when these particles strike the shielding) are the least studied and studiable on earth in terms of radiobiological effects[40].

GCR appears to be relatively constant in deep space outside the magnetosphere. It is isotropic. It contributes about 4 microrads per hour at sea level[39]. Its flux is maximal at solar minimum, the phase in the solar cycle where the solar "wind" (SCR) and the interplanetary magnetic field it creates are weakest. At altitudes up to 600 km it varies from 1.7 millirad/day at 0 degrees orbital inclination to 6.7 at 90 degrees inclination, or polar orbit[45]. As the Air Force is planning a series of polar shuttle flights, this will create a small, for short flights, increase in crew members' dosages. With increasing altitude this differential is slightly greater. GCR is measured when its HZE particles strike tissue or shielding, generating neutrons, protons, alpha particles, and other radiation[39]. It is presumably these particles which caused the flashes of light seen by the astronauts after dark adaptation[13,24]. Although GCR on interplanetary flights would probably be only around 13 rads annually at solar minimum, its QF could be as high as 5 or more[8]. In fact, for HZE radiation impinging directly on the body, concepts like RBE and QF, which currently figure prominently in dose protection requirements, become meaningless owing to the tremendous amounts of energy deposited in very small amounts of tissue. GCR is difficult to

shield against; the half-value layer (thickness of material required to reduce the intensity of radiation by one half), or HVL, for GCR is about 100 g/cm^2 of shielding[45]. This is of course prohibitive. In addition, the thicker the shielding, the higher the probability of generation of secondary radiation.

The most hazardous source of radiation is the sun. This is not so much from SCR as from solar flares, which are solar electromagnetic "storms." These are unpredictable and, for certain orbital and lunar flights, do not give adequate warning time for mission termination and return to earth. On 23 February 1956 a solar flare caused about 100 millirem/hour as low as 35,000 feet[39]. In space the dose outside the spacecraft could reach up to 900 rems/hour; the $LD_{50/30}$ in man is roughly half that[38]. Fortunately the protons are of 10-500 MeV range[32]; one g/cm^2 of shielding will provide 80% protection, and 10 g/cm^2 99%[38]. Since solar flares are highly anisotropic, it is feasible to provide heavy shielding for a small portion of the craft (a "storm shelter", literally.)

Although an individual flare is unpredictable, they tend to cluster around the solar maxima, with a few surprises, though. They last only a few hours, though sometimes up to two or three days[12]. For radiation safety on interplanetary and long mission flights one has to determine launch dates based on the probabilistic frequencies of flares depending upon the time in the solar cycle. Even so, a three-year trip to Mars could give a probable dose of about 1000 rads under best launch date conditions, and three times that under worst[33,38].

The South Atlantic Anomaly, where the VARB dips toward the earth for currently inexplicable reasons, creates a hazard for earth orbital flights. Trapped protons with energies over 30 MeV come as low as 160-320 km here, instead of approximately 1300 km altitude elsewhere. In the initial Shuttle flights at 38 degree inclination, 6 orbits traversed the anomaly, while 11 were outside it. Maximum flux here was 40-50 times the average daily flux. The Skylab flights noted that the radiation flux encountered was too high for solar or albedo neutrons, or GCR striking the spacecraft; they concluded it was from protons in the VARB[32].

Not only is the external radiation environment quite variable, but so is the radiation distribution inside the spacecraft. On Salyut-4 one cosmonaut received 240 millirads, one received 410[17]. During Apollo-14 the type of mission performed (Commander vs. Lunar Module Pilot), would vary the dose received as much as 10-20%, depending upon where measured[33]. With extravehicular activity the reduced shielding and abrasive effects of the space suit can create electron irradiation, which is absorbed mainly in the skin at these energies, and cause radiation dermatitis. Clearly the need for personal as well as spacecraft dosimetry is needed.

Even if the entire space radiation environment were well known, and the biological effects of the various radiations understood from terrestrial experiments, there are several factors encountered is space flight known to affect the radiation response.

Some of these are synergistic, some antagonistic. An excellent summary is contained in the Bioastronautics Data Book[33]. For instance, chronic acceleration improves radiation tolerance, acute acceleration decreases it. Hypoxia, both acute and chronic, is radioprotective; oxygen-rich atmospheres act as radiation sensitizers. Microwave and ionizing radiation effects are additive in dogs. Prolonged weightlessness, which can be encountered only in space, creates decreased energy expenditure, decreased erythrocyte mass, fluid shifts, cardiovascular deconditioning, increased fatiguability, and bone decalcination. Most of these, when studied in isolation, decrease radiation tolerance[18]. There are certain vitamins and chemicals which, in the Russian literature chiefly, have been shown to improve radiation tolerance. Grigor'yev's excellent review article summarizes these, as well as most other radiobiological aspects of space flight[18].

Recommended radiation exposure limits have been set, based on a variety of criteria. For 30 days the recommended whole body dose at 5 cm depth is 25 rem; this figure has been shown, in Russian studies of whole body irradiation on experimental subjects[18], to be well below the risks of radiation-induced gastrointestinal problems which might adversely affect the mission. Four hundred rem was the National Academy of Science estimate of the doubling dose of the incidence of leukemia, the most sensitive malignancy to radiation induction. This was set as the career dose; quarterly and yearly maxima of 34 and 75 rem were calculated using this as the reference[32]. Current occupational and non-

occupational standards are 5 and 0.5 rem whole body irradiation annually; the increased standards for astronauts are based on the increased unavoidable exposure risks, their superb general health, and the importance of the mission.

Specific questions that must be answered are what the incidence of cancer and diabetes for past and future astronauts will be. Are the current NASA (National Aeronautics and Space Administration) standards too restrictive, or will they in time be shown to permit a much higher than expected incidence of these and possibly other conditions? Can these rates be related to the doses from photon, proton, and neutron radiation? These questions have not been answered to date, nor indeed is it possible to answer them on the basis of terrestrial human studies or Skylab-type animal experiments. The only way to adequately assess the radiation hazards of space flight is through a longitudinal prospective study of the long term effects of space radiation exposure.

METHODS

The most appropriate study design is a long term descriptive surveillance study with appropriate statistical analysis annually. The paradigm of studies relating dose exposure to long term radiobiological effects is the work done by the Atomic Bomb Casualty Commission (ABCC) post World War 11 and its successor in 1975, the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. Briefly, the data stem from the careful followup of persons exposed to nuclear weapons detonation and their children for neoplasms, birth defects, and several other conditions[1,5,11,26,29,35,44,47]. Radiation exposure of the survivors is of course difficult to estimate, and there have been several revisions of dose estimates[25]. Nonetheless several studies correlating the incidence of various malignancies with respect to person-years of exposure and ranges of doses received have been performed, with generally good corroboration with other studies of long term radiation effects in patients and workers.

The ABCC was established a few months following the war and went to Japan in spring 1947. The Japanese National Institute of Health began cooperation the following year. Patients were contacted at home by trained interviewers who collected massive amounts of biographical data including marital, occupational, residential and educational background, as well as where they were at the time of bombing (ATB), if they were shielded, what protective clothing if any they were wearing, etc. A complete family and

personal medical history was taken plys physical and, in children, anthropometric examinations and selected laboratory tests, with special studies as indicated[42]. For the Life Span Study (LSS), which was intended to see if there was a dose-related reduction in life expectancy as well as get leads for more specific future investigations[5], 28,000 survivors less than 2 km from the hypocenter ATB, 16,000 from 2-2.5 km, and 9,000 exposed persons beyond this range were selected. Family and neighborhood registries were used to help identify and locate possible survivors. This effort was complicated by the mass migrations, chaos, and panic during the post-bomb period. Controls with similar age ATB and sex were selected. Follow-up data was collected from death certificates. Persons in the Adult Health Studies, studies intended to measure dose-related disease incidence rates plus subclinical laboratory changes and nonspecific potentially radiation-related effects, were selected from residents of Hiroshima and Nagasaki permanently domiciled there in October 1950. Four groups of persons, about 5000 per group, were selected from persons exposed less than 2 km from the hypocenter and acutely symptomatic post explosion, persons less than 2 km but essentially asymptomatic, those at greater distances, and persons not residing in these cities ATB[11]. Conclusions from studies using these study designs have been faulted because of the small sample sizes! Careful examinations at annual or biennial intervals were performed to provide data.

These studies, based on outcomes of a single high-dose

exposure, are very helpful to the goals and design of the present proposal. First, no life-shortening or excess mortality was noted once neoplastic disease was excluded, and therefore will not be studied here[11,47]. An excess of developmental anomalies and genetic defects in the first generation born to bomb victims (excluding persons in utero ATB) has not been seen to date[47] and therefore will not be addressed. Also, no statistically significant increase in the frequency of individuals with chromosome abnormalities attributable to parental radiation exposure has been found[2]. Death certificate data alone is not entirely reliable; although diagnostic accuracy for breast and cervical carcinoma was over 90% and over 80% for leukemia, it was less than 70% for about half of all other neoplasms studied[5]. Another study[26] noted a marked underascertainment bias for diagnosis of breast carcinoma owing to outmigration of younger women from the bombed cities, as well as from the fact that breast cancer, though a serious disease, is not always the cause of death. When LSS death certificates were reanalyzed for breast cancer as a complication or contributing condition, and not solely as the underlying cause of death, about twice as many cases were found. These authors recommended studying the incidence of this disease rather than mortality, which this proposal will do for all malignancies plus diabetes. The use of underlying vs. multiple cause data may account for the fact that some studies claim a detectable increase in this disease after only 16 or 19 rads[5,26], and other studies showed no difference between women less than 5 km from the hypo-

center ATB and those further away[11]. Death rates of those in Hiroshima and Nagasaki receiving little irradiation, and persons not in the city ATB, were similar to the national background[11]. There is definitely a carcinogenic effect related to total dose received, age ATB, sex, and other variables. What these studies have not answered is the effect of modifying factors such as smoking and diet on disease incidence, or possible differences arising from the different types of dose received[47].

A prospective study of the astronaut population will avoid some of the recognized pitfalls that have plagued the ABCC and RERF work. Dosimetry, when measured prospectively and, as far as possible, by type of radiation received, will be much more useful; frequently the bomb studies use "intervals probably smaller than dose measurements precision would justify[44]." Setting up of a tumor registry initially, or at least while the sample population is very small, will avoid the sole reliance on death certificate information. Tumor registries were not formally set up in these two cities until the mid-50's; it was noted that the Nagasaki Leukemia Registry noted 32 cases in 1950-1954, while the LSS study included only nine[5]. Prospective planned data collection is certainly much more reliable than retrospective review.

Currently NASA provides paid extensive annual physical examinations for all astronauts selected into the program[14], whether or not they have flown. Almost complete followup occurs at present. In addition, a computerized data base records all radiation received during flight, as well as in diagnostic workups

preflight. The physical examinations, including an annual treadmill study, continue after retirement for the astronauts who have flown, again with almost complete followup.

NASA has also identified 5 Civil Service employees employed at Johnson Space Center for each astronaut. These controls, or comparison subjects, began employment about the same time as the astronaut was selected into the program. Controls are matched for age, sex, height/weight index, and, to some extent, activity level. They are also matched for smoking patterns, although very few of the astronauts smoke. Some of the control subjects serve as comparison subjects for more than one astronaut; overall there are about four times as many controls as astronauts. These people receive an occupational health examination annually that closely parallels that of the astronauts, though with fewer selected blood studies and with a treadmill test triennially. Currently there are plans to offer these examinations free of charge post retirement, if the subject pays transportation to the Space Center.

The population for study will be all future American astronauts, those who have flown above 50 nautical miles, where aerodynamic control is no longer effective, plus the comparison subjects. Data will also be collected from those astronauts who have already flown and who number about 60 as of November 1982. One hundred twenty-seven persons have been selected into the program, of whom about 50 are still active. The Air Force currently has "booked" one-third of Shuttle flights over the next decade[46]. By 1990 about 200 persons will have flown in about 400

Shuttle, or Space Transport System (STS), flights[32]. When the planned space station is set up, it will be staffed by crews of 17 persons rotated every six months. All these astronauts and comparison subjects will be followed for life. Currently, although Soviet data is reviewed, data from their cosmonauts are not included in NASA studies.

Preflight data collected from both astronauts and the comparison subjects will be age at first flight (for the astronauts), sex, a copy of the preflight or occupational physical, and previous occupational and diagnostic exposure history. Attempts to ascertain radiation exposure from previous diagnostic workups for both astronauts and controls will be made based on their previous disease and hospitalization histories. During flight dosimetry will be recorded using the personnel dosimeters and survey meters used by NASA in the Apollo and Skylab programs [3,31,40]. These will record total doses and component doses from neutron, proton, photon, and possibly HZE radiation. The flight pattern will also be recorded with respect to orbital inclination, passage through the South Atlantic Anomaly, traversing of the VARB and the earth's magnetosphere.

Consent from astronauts to allow recording and filing of data will of course be obtained prior to data collection. Informed consent procedures for collection of dosimetry and other personal and medical data are already established at NASA. It will be stressed that dosimetry data for astronauts still active will remain confidential and will not be used as an

independent criterion for determining eligibility for further missions. This item was of particular concern even from the beginning of the space program[32].

Personal dosimeters have not always been worn, though only a few flights had little or no dosimetry devices, either personnel or crew, aboard. Fortunately the orbits, flight patterns, and time during the solar cycle can be fairly well reconstructed. Although radiation exposure within the spacecraft, depending on internal shielding, varies, an average dose can be given to unbadged personnel. In the future all crew members will have personal badges. The reliability of dosimetry data will be much greater than that used by the ABCC and RERF, whose data nonetheless gave meaningful results. It should be noted that astronauts from all the Mercury, Gemini, Apollo, Skylab, and the first three STS flights received less than 2 rads, except on Skylab 3 (4.7 rads) and the 84-day Skylab 4 mission (7.8 rads). But the diagnostic exposure for each crewmember's preflight workup was between 2 and 3 rads! Hence diagnostic exposure will be recorded as much as possible.

The problem of dealing with influences from other potential carcinogens (background radiation exposure, other occupational carcinogens, smoking, diet) is a difficult one. Occupational radiation protection standards, national and international, deliberately disregard exposure received from medical diagnostic procedures and variances in natural background. They also do not take the worker's lifestyle (e.g. cigarette smoking)

into account. Background radiation, which is similar to space radiation in its chronic low dose and low dose-rate nature, varies considerably throughout the United States and the world. In some areas such as in Brazil, India, and Southern France people get from 5-10 rads per year; yet no sound epidemiologic data has ever shown increased mortality, miscarriages, malignancy, or altered fertility index or sex ratio[27]. People in Denver receive more radiation (0.2 rad) annually than the astronauts in each of the Gemini missions except Gemini 10[32]. It is unlikely that any increased incidence of cancer or diabetes from space radiation from photons will be detectable at these dose ranges. Neutrons, protons, and HZE particles are not encountered in the diagnostic or natural background settings.

The possible additive or synergistic effects of smoking and occupational carcinogens other than radiation are very difficult to assess. This information will be requested and recorded, though will not be analyzed until and if enough astronauts accumulate high enough exposures to show an increased incidence of certain malignancies. The appropriate procedure at that time would be to stratify the data to see if the association is stable when nonsmokers and smokers are considered separately. This will not be done in the early analyses. It should be noted that Beebe[5] felt that case-control studies were useful for variables for which observations didn't exist on the cohorts.

The post-flight questionnaire (Appendix) will be sent annually to all comparison subjects and any astronauts who didn't

receive a physical examination from NASA that year. With prior permission, copies of hospital record face sheets, pathology reports and slides, retirement or discharge physicals, and correspondence with physicians and health physicists (or similar personnel) at diagnostic radiology facilities, should the subject have received diagnostic X-rays will be obtained as the need arises. Currently there are proposals within NASA to offer free examination to those consenting to serve as controls for the astronauts; if this is done, the questionnaire will be sent only to individuals not availing themselves of the exam. Supporting physician information will be used to corroborate positive reports. Currently almost all astronauts return for the annual physical, so lack of compliance is not now nor likely to become a problem. Should this occur, however, the physician in charge of the study will hopefully be able to use death certificate information, which is a public record and can be requested, to obtain some data.

Dosimetry data will be obtained and kept at NASA. This will be broken down into estimated or actual photon, proton, neutron HZE, and total doses. Appropriate dose intervals will be determined at time of analysis. Copies of the medical examinations noted above, physician correspondence, laboratory and histopathological forms, consultation reports, reports from the health physicist in charge of facilities where any diagnostic films were taken concerning probable exposure, and death certificates will also be kept. The International Classification of Disease, 10th edition, will be used to numerically code all diagnoses of neo-

plasms (by type and in aggregate), and diabetes; other diseases will be classified as "other" with an appropriate number for computer coding. Since eventually a large amount of data will be collected, consultation with computer support services at NASA will be obtained after study approval to design coding of preflight data, dosimetry data, diseases incurred, and dates of incidence. A dedicated consultant will be needed initially; subsequent training of secretarial personnel to encode questionnaire, disease incidence and death certificate data should take only a few hours and can be done by the program coordinator or research assistant.

The statistical methods involved will be rather complex, and consultant aid will be necessary every time reports and formal papers are planned and generated. At any time of analysis most data will be censored. Many life-span studies of atomic bomb survivors rely on modifications of the Mantel-Haenszel procedure for the construction of contingency tables using Cochran's method for determining chi-squared values. Trend analyses using complex regression models are employed, as frequently no "control" group is used and the population receiving less than 5 rad is used as the baseline[34]. An excellent discussion by Whittemore and McMillan [51] summarizes the pros and cons of three types of analysis used in occupational mortality (here, disease incidence) studies: the person-years method, the cohort method, and the case-control method. They analyzed data from uranium miners for lung cancer mortality related to total working level months of exposure and smoking

exposure, and described extensively the statistical procedures used in the latter two methods especially.

The person-year method is by far the simplest statistically, with relatively low model dependency. All astronauts and comparison subjects would be followed from date of first flight until death or diagnosis of cancer or diabetes. Each year of followup would be allocated to one of several mutually exclusive and exhaustive categories, determined by age, decade of birth, sex, and cumulative radiation exposure (in aggregate and by component radiation.) Each case of cancer or diabetes would be assigned to exactly one category, depending upon the patient's status at time of diagnosis. Total person-years in that category are then used to determine the incidence rate. Using the "expected" number of cases for each category, which will be calculated using risk estimates compiled by the Biometry Branch of the National Cancer Institute[42] for the probability of a person in that category eventually developing cancer in his or her lifetime, the ratio of observed to expected cases can easily be calculated. For example, consider an astronaut born in the 1950's who received 10 rads on a flight this year, who was age 30 at time of flight, and who will eventually contract leukemia at age 60. He will contribute 5 person-years to the 20-35 age range, 15 to the 35-50, and 10 to the 50-65 range. He will not be counted as an observed case for the first two age groupings, but will for the third. The major drawback to this method is obvious. Assuming the earlier estimate of one case per rem per 10,000 person-years is low by an

order of magnitude, it would take 100 persons contributing 10 person-years to this age range, born in the '50's, and receiving this dose to get one increased case over the "expected" incidence. To date, only one person of the astronaut corps has died of cancer, and he received very little radiation.

The cohort and case-control methods both assume that occupational exposures act multiplicatively on age-specific incidence rates. The cohort method has more power and efficiency, valuable in small sample populations such as this one, but is rather computer-intensive. Briefly, an individual's cause-specific incidence rate would be estimated as

$$\lambda(t;\underset{\sim}{z},s) = \lambda(t;\underset{\sim}{0},s)\rho(\underset{\sim}{\beta},\underset{\sim}{z})$$

where t is the astronaut's age, and s a stratum of "nuisance variables" such as year of birth. The covariate vector $\underset{\sim}{z}$ is a function of risk factors which may vary with time, $\underset{\sim}{\beta}$ a vector of unknown parameters which may vary between strata, and ρ a non-negative function of $\underset{\sim}{\beta}$ and $\underset{\sim}{z}$. The "relative risk" function ρ is usually in exponential form

$$\rho(\underset{\sim}{\beta},\underset{\sim}{z}) = e^{\underset{\sim}{\beta}'\underset{\sim}{z}} .$$

$\underset{\sim}{\beta}$ is estimated by maximizing a product of "partial liklihood terms, one for each case. The term for the i^{th} case is

$$\rho(\underset{\sim}{\beta},\underset{\sim}{z}_{i0}) \Big/ \sum_{l \in C_i} \rho(\underset{\sim}{\beta},\underset{\sim}{z}_{il}) ,$$

where C_i is a "risk set" consisting of the astronaut and those astronauts in stratum s outliving his age at diagnosis, $\underset{\sim}{z}_{il}$ the covariate for the l^{th} astronaut in the i^{th} risk set, and $\underset{\sim}{z}_{i0}$ the case's covariate[51]. Obviously such an analysis is quite complex,

requiring computer and statistician consultant support, and is clearly model-dependent. Fortunately this support is available at NASA.

DISCUSSION

In this country one of the major recent concerns of occupational medicine has been carcinogenesis from hazardous materials and practices in the workplace. In the intitial phases of the space program physicians were obviously more concerned with factors which were capable of causing injury or death during or soon after flights. As experience and knowledge in space physiology and medicine were gained, and long term space stations and interplanetary manned flights became more and more possible from a physiological point of view, concern for conditions with long latent periods grew. Grigor'yev's excellent review summarized Russian medical concerns regarding radiation-related performance disorders as being threefold: 1) immediate or early reduction of efficiency, 2) progressively increasing reduction of work capacity due to dose accumulation, and 3) probability of late radiation reactions that could affect further flights or cut short extended stays on a planet. Maximum permissible doses, defined as doses which in light of current knowledge "cause only a very slight chance of severe somatic and genetic effect," are set on these bases[18]. To these must be added the probability of developing late effects that, though they do not affect an astronaut's career or mission performance, do affect his or her life span and health. However, these are the effects that, owing to their long latent periods, normally low risk, and occurrence in the non-irradiated population, require painstaking analysis that

will stretch over several decades. Based on the nuclear weapons experience, and on the unexpected increase of diabetes in proton-irradiated monkeys, it is most advisable to study the long term incidence of cancer, as well as diabetes and other potentially life-threatening or debilitating conditions.

The lifetime risk at birth of both developing and dying from cancer has increased from 3-5% from 1975 to 1985, depending on race and sex[42]. For white males age 35 the risk of eventually developing invasive cancer is 37.3%. This risk is 36.8% at age 20, and still 37.3% at age 50. For black males the risks at ages 20, 35, and 50 are 35.6, 37.0, and 38.7%. For white females the risks are 34.2, 34.0, and 31.9%; black females have roughly 4% less risk at each age[42]. It would be ethically impermissible to not make an attempt to ascertain the increased hazard that space radiation poses. For reasons cited above, a prospective longitudinal descriptive study is the only way to do this.

Because of the natural risk of cancer, the relatively low doses encountered in current missions, and the long latency period for most cancers, especially at lower doses, the cohort sizes needed to demonstrate significant increased risks at various dose levels are much higher than the current astronaut population. Though their numbers will increase rapidly in the next few years, it will be some time before the sample size is large enough to allow valid recommendations. Therefore this project will have to span several decades and require an ongoing uninterrupted committment to the study outlasting the careers, and perhaps the lives,

of the initial investigators. Nevertheless the study must be done. The sooner it is established, the more reliable the data will be and the more valid the eventual findings.

GLOSSARY

Albedo: Reflected radiation. In the case of neutrons this results from particles striking the atmosphere; neutrons reflected back into space are albedo neutrons.

Fractionation: The term used in radiation therapy to describe in what size increments the total dose was given, how many increments, and the total elapsed time between first and last doses.

Galactic Cosmic Radiation (GCR): The flux of high energy particles emanating from regions outside the solar system.

Heavy energetic particles (HZE): Ions of atomic number greater than 2 that travel at very high velocities.

Inclination: This describes, in degrees latitude, how far an orbiting body extends north and south of the equator. Objects in polar orbits have, by definition, 90 degree inclinations.

Isotropy: When particulate irradiation flux upon an object is equal from all directions, the radiation is considered isotropic. This is usually the case with GCR and in the VARB. Solar flares, however, are anisotropic, with the sunward region obviously receiving the greatest flux.

$LD_{x/y}$: The dose required to kill x% of the species studied within y days.

Linear energy transfer (LET): The rate at which charged particles created by the specified radiation deposit energy

over a specified length in a medium. Usual units are KeV/micron (KeV is kilo electron volt).

Magnetosphere: The magnetic cavity around the earth created by its magnetic field as it moves through space.

Quality Factor (QF): A correction factor that attempts to relate the physical dose in rads from one type of radiation to the dose in rads required to produce the same biological effect. The standard of reference (QF of 1) is gamma radiation.

Rad (radiation absorbed dose): The unit of dose, which is energy deposited per unit of mass. 1 rad is 100 ergs/gram. In the International System of Units (SI), 1 Gray, or 1 joule/kg, equals 100 rads.

Relative biological effectiveness (RBE): Defined by the quotient of the dose of 250 KeV X-rays divided by the dose of the test radiation to produce the same biological effect.

Rem (radiation equivalent man): The unit of dose equivalent used in radiation protection. The new SI unit is the Sievert, which corresponds to 100 rems. The rem dose equals the rad dose times the QF. The rem is an "artificial" entity in the sense that it cannot be measured, as can physical dose. It is an estimate used to help define permissible dose limits.

Shielding: Material used as part of the exterior or interior of the spacecraft that attenuates radiation. It is usually measured in terms of equivalent grams aluminum per square centimeter surface area required to attenuate radiation to

the degree specified, rather than directly measuring thickness per se.

Solar Cosmic Radiation (SCR): Cosmic radiation, like GCR, except that it arises from the sun. It is 85% protons, 14% alpha particles (helium nuclei), and less than 1% HZE.

Solar cycle: SCR varies in a sinusoidal pattern over a roughly 11-year period. At times there are unpredictable releases of unusually large amounts of radiant energy called solar flares. GCR tends to vary inversely with the maxima and minima of solar cycles.

South Atlantic Anomaly: A discontinuity in the earth's geomagnetic field, from approximately 0-60 degrees west longitude and 20-50 degrees south latitude, where there is a markedly increased flux of trapped protons. This creates an increased hazard for orbiting spacecraft.

Van Allen Radiation Belts (VARB): Regions of high-energy particles presumably emitted by the sun and trapped in the earth's magnetic field. The belts are doughnut-shaped and centered about the earth's magnetic field. There are two main belts, an inner (roughly 300-1200 km, depending on latitude) and an outer (10,000-55,000 km.)

APPENDIX

ANNUAL QUESTIONNAIRE

Dear (name):

As you are aware, the National Aeronautics and Space Administration is conducting an ongoing study to assess the long term effects of radiation encountered in space. The purpose of the study is to see if there is an increased risk in astronauts exposed to space radiation, relative to the general population, of contracting cancer or other serious illnesses, including diabetes, related to the dose of radiation received while in space. NASA is collecting data on all astronauts, as well as selected non-astronauts of the same age, sex, size, and activity level, for this purpose. Data includes exposure to radiation, both diagnostic and occupational, incidence of malignant diseases and diabetes, smoking history, as well as age at time of space flight and types and doses of radiation absorbed during flight. People in the study are being followed annually, hence this questionnaire. It would help this study very much if you would take a few minutes to answer the following questions:

Have you seen a physician the past year for other than minor illnesses or routine physical examination? If so, may we contact the physician regarding his or her findings and diagnoses? Please provide the physician's name, office address, and phone number.

Have you been hospitalized during the past year? If so, where? May we request a copy of the hospital face sheet (the single page of your hospital record that contains the diagnoses and procedures performed during hospitalization)?

During the past year have you been told by a physician that you have leukemia, lymphoma, cancer, diabetes, or other major illness not previously diagnosed? If so, what was the diagnosis?

Have you had any X-rays taken during the past year? If so, may we obtain information from the health physicist in charge of the facility regarding the probable dose received? Please give the facility's name and address, or that of the physician who ordered the study.

Do you smoke? If so, how much?

Would you like to make any other comments concerning your health the past year?

Thank you very much for your cooperation. Should you desire more information, or if you would like a copy of any scientific publications arising from the study to date, please feel free to contact:

(name, address, phone)

Sincerely,

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VITA

Glen Irving Reeves was born in Chicago, Illinois, on December 23, 1946, the son of Harry Irving and Ruth Elnora Miller Reeves. He was raised in Weiser, Idaho, and graduated from Weiser High School in June 1964. That fall he matriculated at Columbia College of Columbia University in the City of New York and received his B.A. in June 1968 with a major in mathematics. He began studies that fall at the College of Physicians and Surgeons of Columbia University and received the M.D. degree in June 1972. He completed two years of internship and residency in General Surgery at Barnes Hospital in St. Louis on June 30, 1974. After a six-month American Cancer Society Fellowship in Surgical Oncology and six months as an emergency room physician at Missouri Baptist Hospital in St. Louis, he began a residency in Therapeutic Radiology at the Edward Mallinckrodt Institute of Radiology, Washington University, St. Louis. He completed his residency and received board certification in Therapeutic Radiology from the American Board of Radiology in December 1977. After six months as an Instructor in Radiology at Washington University and Barnes Hospital he entered active duty in the United States Air Force. Currently he is stationed at Wright-Patterson Air Force Base, Ohio, with the rank of Lieutenant Colonel. He married the former Jane Corwin in 1970. They have two children, Michael Glen, born in 1973, and Sarah Ruth, born in 1976.

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